

An Inkling of Suspicion

Prenatal Exposure to PBDEs and Neurodevelopmental Impairment

A longitudinal cohort study of more than 150 U.S. children conducted over 7 years associates prenatal exposure to higher concentrations of polybrominated diphenyl ether (PBDE) flame retardants with lower scores on tests of neurodevelopment [*EHP* 118:712–719; *Herbstman et al.*]. This is the second recent epidemiologic study to link PBDEs with evidence of adverse effects on brain development, although differences in methodology between this and the other study [*EHP* 117:1953–1958; Roze et al.] make direct comparisons difficult.

PBDE flame retardants have been used for decades in a wide variety of goods, including automobile and airplane components, electronics, and home and office furnishings. The toxicologic evidence linking PBDEs to adverse health effects led the European Union to use the precautionary principle as the basis for banning all three PBDE formulations (penta, octa, and deca). In the United States, manufacturers voluntarily discontinued the penta and octa formulations in 2004 and have agreed to phase out deca by the end of 2012.

The mothers of the children in the current study were pregnant at the time of the World Trade Center (WTC) attacks in 2001 and gave birth at a hospital within 2 miles of the WTC site. The women were recruited for a study on the effects of exposure to compounds in dust from the decimated towers. PBDEs were measured in the cord blood of 210 infants, and 152 of these children later participated in at least

one round of neurodevelopmental testing conducted at 1, 2, 3, 4, and 6 years of age.

The children with higher levels of exposures consistently had, on average, lower developmental scores at each time point compared with less-exposed children; the association was particularly evident at age 4 years. The researchers were not able to evaluate associations with developmental delay because few children had developmental scores low enough to meet the criterion for this outcome. However, in many cases average test scores in children with exposures in the highest 20% were 5–11 points lower than average scores for less-exposed children.

Although some evidence suggests the PBDE exposure seen in the children could be related to the WTC attack, the authors say “it is certain” that sources other than the WTC contributed to the PBDE levels in the infants’ cord blood. Because the levels observed in these children were similar to those reported in other U.S. populations, the new research suggests the observed effects could be widespread.

According to the authors, these findings are consistent with reports of hyperactivity and learning and memory deficits in experiments with mice exposed neonatally to PBDEs. Other work, most recently a laboratory study using human cells [*EHP* 118:572–578; Schreiber et al.], suggests PBDEs may interfere with thyroid hormones critical for normal brain development. The authors point out that additional studies exploring associations between PBDE exposure and developmental effects are under way. In the meantime, they say identifying opportunities to reduce people’s exposure to these compounds should be a priority.

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Organochlorines and Prostate Cancer in Japan

No Link in Men without Occupational Exposures

Occupational exposure to organochlorine compounds during pesticide manufacturing or application has been associated with prostate cancer incidence. However, prostate cancer was not clearly associated with plasma levels of organochlorine compounds among Japanese men in the general population, according to results of a large-scale prospective study [*EHP* 118:659–665; Sawada et al.].

Organochlorines can act as endocrine disruptors. Studies in animals and humans have reported evidence of associations between

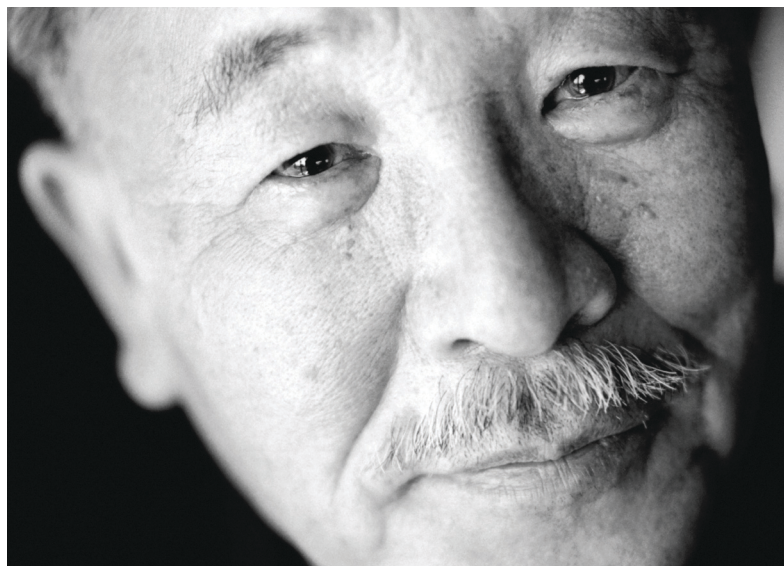
significant environmental exposures and effects such as urogenital malformation in boys born to agricultural workers. Organochlorines were banned in the 1970s in Japan, where the current study was based. However, because these compounds persist in the environment, environmental exposures may still be affecting human health.

In a nested case-control study, the authors tracked the incidence of prostate cancer among 14,203 men aged 40–69 who were enrolled in a prospective study through the Japan Public Health Center. Participants responded to baseline health questionnaires and provided blood samples between 1990 and 1995; they were followed through 2005. The authors identified 201 participants who were diagnosed with prostate cancer during the period of the study, each of whom was matched with two controls from the study cohort. The baseline blood samples from these 603 men were analyzed for polychlorinated biphenyls (PCBs) and several organochlorine pesticides.

The authors found no statistically significant associations between blood levels of any organochlorine and prostate cancer. Contrary to expectations, men who developed cancer had lower blood levels of the pesticides hexachlorobenzene and β -hexachlorocyclohexane than men who did not develop cancer, though these inverse associations were not statistically significant.

Strengths of the study include the large number of participants and the use of biological samples collected many years before diagnosis. However, the authors acknowledge the small number of cases of prostate cancer may have limited their ability to detect associations with organochlorine exposures. Moreover, the length of followup may have been insufficient to fully detect incidence of prostate cancer, which is generally slow to develop.

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Pregnant Pause

Does Maternal PBDE Exposure Extend Time to Pregnancy?

Animal studies indicate polybrominated diphenyl ethers (PBDEs) are endocrine disruptors, potentially affecting the role of thyroid hormones in regulating the reproductive cycle and fertility. The compounds also have been associated with delayed puberty and altered estradiol levels in female animals. Very little is known about the potential effects of PBDEs on human reproductive health, though, and a new study is the first to characterize a specific concern—a relationship between PBDE blood concentrations and a delay in achieving pregnancy [*EHP* 118:699–704; Harley et al.].

PBDEs are used as flame retardants in furniture, carpeting, textiles, electronics, and plastics. Commercial mixtures of PBDEs contain a variety of congeners, or chemical variations. Data collected by the Centers for Disease Control and Prevention suggest 97% of Americans may have detectable levels of PBDEs in their blood.

The current study included 223 pregnant women enrolled in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a longitudinal birth cohort study focused on environmental exposures and reproductive health in California's Salinas Valley. Upon enrollment, the women reported their reproductive history, previous use of contraception and fertility medication, whether the pregnancy was planned, and how long it took to become pregnant after stopping contraception.

Blood samples collected around 26 weeks of pregnancy were analyzed for 10 PBDE congeners. Statistical analyses focused on those most commonly found: BDE-47, BDE-99, BDE-100, and BDE-153. BDE-100 and BDE-153 were the most strongly associated with longer time to pregnancy. For each month,

the likelihood of becoming pregnant was 40% or 50% lower with a 10-fold increase in concentration of BDE-100 or -153, respectively. With a 10-fold increase in the total of all 4 congeners, there was a 30% decrease in the odds of pregnancy each month.

The study relied on self-reported time to pregnancy, which is subject to a number of biases. In addition, the study's findings are limited to 4 PBDE congeners and may not extend to a broader population. Consequently, further research incorporating more congeners and a more representative population is needed. However, given the likelihood of PBDE exposure in the general population, even a small effect of these chemicals on fertility may affect a large number of individuals.

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Cancer Collusion?

Dietary Fat May Modify Dioxin-Induced Mammary Cancer Risk

Some human and animal studies have linked early-life exposure to the endocrine-disrupting chemical 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) with an increased susceptibility to breast cancer. Dietary fat has been posited as another potential risk factor for breast cancer, possibly acting through the estrogen pathway. A new animal study suggests a high-fat diet may alter estrogen metabolism, thereby modifying the effects of maternal exposure to TCDD and increasing mammary cancer risk in the next generation [*EHP* 118:596–601; La Merrill et al.].

One group of pregnant female FVB/NJ mice (a TCDD-responsive mouse strain) received an olive oil/toluene blend with TCDD; another received an equivalent volume of olive oil/toluene without TCDD. Their female offspring were randomly assigned to either a low-fat or high-fat diet and exposed to the carcinogen 7,12-dimethyl-benz[*a*]anthracene (DMBA) at days 35, 49, and 63 after birth in order to initiate mammary tumors. A second cohort of female offspring was treated identically until either day 35 or 49, when morphologic and molecular analyses of their mammary glands were performed.

Maternal TCDD exposure was associated with a doubling of mammary tumor incidence only in offspring fed the high-fat diet.

In contrast, no mammary tumors arose in mice exposed to TCDD *in utero* and fed the low-fat diet. Whereas one-third of TCDD-unexposed litters fed a high-fat diet had DMBA-induced mammary lesions, every litter exposed to both TCDD and a high-fat diet developed mammary lesions.

Previous animal studies had shown that prenatal exposure to TCDD alters mammary gland differentiation and increases susceptibility to mammary cancer. However, this is the first to show that TCDD may interact with a high-fat diet during pregnancy and early life. The researchers propose that a high-fat diet may boost sensitivity to maternal TCDD exposure by altering estrogen metabolism.

The new findings highlight a possible mechanism that may explain epidemiologic data separately linking early-life TCDD exposure and high-fat diets to increased breast cancer risk in humans. In the present study, TCDD exposure *in utero* combined with a high-fat diet was also associated with increased expression of *Cyp1b1* and decreased expression of *Comt* in mammary tissue. Human studies have suggested that diminished *COMT* expression and increased *CYP1B1* expression are associated with increased risk of breast cancer and other estrogen-responsive cancers, perhaps by increasing levels of estrogen metabolites that can contribute to carcinogenesis by damaging DNA. They also note that obesity may affect breast cancer risk because TCDD persists in adipose tissue, including that in the breast.

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